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THE CHEMISTRY OF OPTICALLY ACTIVE MACROCYCLIC  
POLYETHERS(U) DUKE UNIV DURHAM NC  
R G GHIRARDELLI ET AL. 1985 ARO-11865.2-CH

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ARO-17986.7-CH DAAG29-79-D-1001

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| 1. REPORT NUMBER<br>ARO 17986.7-CH<br>ARO 14800.3-CH  | 2. GOVT ACCESSION NO.<br>NA | 3. RECIPIENT'S CATALOG NUMBER<br>NA   |
| 4. TITLE (and Subtitle) ARO 11865.2-CH<br><br>The Chemistry of Optically Active Macro-<br>cyclic Polyethers   |                             | 5. TYPE OF REPORT & PERIOD COVERED<br>1 Jul 1973 - 31 Dec 1985<br>Final Report  |
| 7. AUTHOR(s)<br>Robert G. Ghirardelli<br>R.A. Palmer  |                             | 6. PERFORMING ORG. REPORT NUMBER  |
| 9. PERFORMING ORGANIZATION NAME AND ADDRESS<br>Duke University<br>Durham, NC 27706  |                             | 8. CONTRACT OR GRANT NUMBER(s)<br>DAAG29-79-D-1001<br>DAAG29-77-G-0052<br>DAAG29-78-G-0054<br>DA-ARO-D-31-124-73-G188<br>DA-AROD-31-124-73-G188<br>DAHCO4-74-G-0207<br>DAAG29-76-G-0080 |
| 10. program element, etc. N/A   |                             | 12. REPORT DATE   |
| 11. CONTROLLING OFFICE NAME AND ADDRESS<br>U. S. Army Research Office<br>P. O. Box 12211<br>Research Triangle Park, NC 27709-2211   |                             | 13. NUMBER OF PAGES<br>8  |
| 14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)   |                             | 15. SECURITY CLASS. (of this report)<br><br>UNCLASSIFIED  |
| 16. DISTRIBUTION STATEMENT (of this Report)<br><br>Approved for public release; distribution unlimited.   |                             | 15a. DECLASSIFICATION/DOWNGRADING<br>SCHEDULE   |
| 17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)<br><br>NA  |                             |   |
| 18. SUPPLEMENTARY NOTES<br>The view, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other documentation.   |                             |   |
| 19. KEY WORDS (Continue on reverse side if necessary and identify by block number)<br><br>Macrocycles                      Crown Ether<br>Macrocylic                      Circular Dichroism<br>Polyethers                      Circularly Polarized Luminescence<br>Ion Pairing  |                             |   |
| 20. ABSTRACT (Continue on reverse side if necessary and identify by block number)<br>Eighteen optically active macrocyclic polyethers, with ring sizes between 12 atoms and 24, were synthesized. In each case chirality was conferred by 2 or 4 methyl substituents on the macro ring. Ten of the compounds incorporated one or two benzene rings, these providing the chromophore which displayed circular dichroism due to the influence of the dissymmetric macro ring fused to them. In other cases the electronic transition either occurred in the cation complexed by the polyether or in an associated anion. Examples of the former were Eu (III) and Tb (III), of the latter nitrate and nitrite. Circular dichroism, circularly |                             |   |

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20. ABSTRACT CONTINUED

polarized luminescence and other techniques were used to probe the nature and extent of the interaction between components of the complex, as well as the conformation of the macrocycle as influenced by complexation.

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THE CHEMISTRY OF OPTICALLY ACTIVE MACROCYCLIC POLYETHERS

FINAL REPORT

ARO PROPOSAL NO'S 11865-CH, 14800-CH, 17986-CH

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1 JUL 73 - 31 DEC 85

U. S. ARMY RESEARCH OFFICE

GRANTS DA-AR00-31-124-73-G-188  
DAHCO4-74-G-0207  
DAAG29-76-G-0080  
DAAG29-77-G-0052  
DAAG29-78-G-0054

CONTRACT DAAG29-79-D-1001

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## Summary

The objectives of this research were to use X-ray crystallography and various spectroscopies, especially circular dichroism, nuclear magnetic resonance and circularly polarized luminescence, to probe the nature and extent of the interaction between macrocyclic polyether complexands and cations, and between the resulting complexes and anions, as well as to determine the influence that complexation exerts on the conformation of the polyether. To accomplish this 18 optically active macrocyclic polyethers (all new compounds) were synthesized, complexation with various salts was accomplished or attempted, spectroscopic measurements were made and the effects of temperature, solvent and anion variation determined. It was found useful to apply other techniques as well as those mentioned above, in order to characterize the molecular species under investigation. These included vapor phase osmometry to establish effective molecular weights, conductance to establish the presence of free ionic species, infrared absorption and Raman spectroscopy to provide confirmatory evidence regarding structure and conformation. Molecular mechanics calculations were carried out to establish a theoretical underpinning for the experimental results.

## Polyethers Incorporating Aromatic Rings

Various macrocyclic polyethers, containing both centers of dissymmetry and a chromophoric group (one or two aromatic rings) were synthesized and it was established that in most instances the circular dichroism spectrum displayed a Cotton effect, and in all instances the CD spectrum was profoundly influenced by complexation with alkali and alkaline earth cations. One systematic study covered three isomeric dimethylbenzo-15-crown-5's (1,2,3) and established the effect on the circular dichroism of changing the location of the methyl substituents while maintaining the 2-fold axis of symmetry. An interpretation was made in terms of the conformations of the uncomplexed macrocycle and the complex with sodium, the cation which has optimum fit with the cavity and therefore least effect on the overall symmetry. (J. Am. Chem. Soc. 1976, 98, 7830; J. Org. Chem. 1983, 48, 2029).

Another systematic study covered three macrocyclic polyethers containing two aromatic rings and two methyl substituents to provide chirality, with the ring size varied (16, 18 and 21-membered) through the length of the bridge in the lower part of the molecule as drawn (4,5,6). Possession of two chromophores introduced consideration of coupled oscillators in explaining the CD results, as well as different orientations of the two aromatic rings. As has generally been true, the maximum strength of the dominant CD band (near 225 nm) occurs when a complexed cation is of a size appropriate to the cavity. This work is the subject of a manuscript in preparation.

A polyether with two fused aromatic rings and three axes of symmetry ( $D_2$ ) was synthesized (7) and its potassium iodide complex subjected to an anomalous scatter structure determination. This established that the configuration at each of the four asymmetric carbon atoms was  $R$ , and since the same precursor was used to prepare the three macrocycles discussed in the previous paragraph, their stereochemistry was confirmed as well. A detailed examination of the high resolution nmr of this compound and its complex with potassium ion was carried out, since each of the four units in the macro contains an identical AA  $BX_3$  grouping of protons.

## Toxicity Studies

Published reports of harmful effects resulting from inhalation of macrocyclic polyethers by laboratory animals caused us to initiate a study of the toxicity (to mice) of 12-crown-4, 15-crown-5 and 18-crown-6 by oral ingestion. The toxicity (as  $LD_{50}$ 's) was moderate, and increased with ring size; the smaller ethers gave evidence of severe neurological effects, and 12-crown-4 in particular was found to cause rapid lysing of red blood cells as well. (Toxicology and Applied Pharmacology, 1978, 44, 263).

## Complexes with Small Cations

Two discoveries facilitated research with small cations (lithium and transition metals). One was that macrocyclic ethers would form complexes with their salts in the absence of solvents which could compete as ligands. Such solvents are often necessary as the initial medium for complex formation because of their ability to dissolve practical amounts of the components. They must then be displaced and removed to leave the complex dissolved in a non-competitive medium. The second discovery was that trifluoroethanol could serve as a useful solvent for solution studies, since it has low affinity for cations and thus is a very poor competitor of the complexand. Crystalline complexes of several transition metals with 12-crown-4 were prepared; that of  $Co(NO_3)_2$  was subjected (by E.M. Holt of Oklahoma State) to an x-ray crystallographic study, as was the 15-crown-5 complex with the same salt, which incorporated two water molecules in its unit cell. (Acta Cryst. 1981, B37, 1080).

## Macrocyclic Polyethers with Vicinal Methyl Groups

Ethyl lactate had been exploited as the optically active precursor of all the previously described complexands, but was soon supplemented by R, R-2,3-butanediol, obtained by microbiological fermentation. The diol was converted into a dimethyl-12-crown-4 (8) as well as the corresponding benzo derivative (9). Limited studies of the former were carried out, and evidence of complex formation with salts of cobalt(II), nickel(II) and copper(II) in TFE solution was obtained from CD activity in the visible region. With dimethylbenzo-12-crown-4 alkali and alkaline earth salts could be employed because of the presence of the aromatic absorption bands; lithium and magnesium perchlorates, with cations fitting snugly into the cavity of the macrocycle, gave the strongest and most distinctive CD bands near 215  $\mu m$ .

A by-product of the synthesis turned out to be the tetramethyldibenzo-24-crown-8 (10) arising from the cyclization of two molecules of each reactant. A series of CD spectra were obtained, in both methanol and TFE, and with salts of both alkali and alkaline earth elements. Interpretation in structural terms is difficult because the large ring is able to assume many conformations around the cations, all of which are significantly smaller than the effective cavity.

## Association with Anions

Our limited success in forming complexes between small cations (lithium and the transition metals) and the 12-crown-4 system led us to the example of cyclam, and the synthesis of a dimethylbenzo-14-crown-4 (11). Its complex with lithium nitrate was prepared as was that of its parent macrocycle, and their structures determined by E.M. Holt. (Acta Cryst. 1984, C40, 394 and 396). When the optically active complex was investigated, it was found to be

soluble in chloroform. In this solvent it gave evidence of ion-pairing between the complexed lithium cation and the anion, since the dissymmetric complexand induced circular dichroism in the inherently symmetric nitrate ion. Interference by the absorption bands of the aromatic ring was eliminated by hydrogenating the latter (to give compound 12), with results confirming the induction of CD, and the dissociation caused by addition of solvents of greater ionizing power. (Tetrahedron Letters, 1980, 21, 1489).

This success led to a series of experiments involving anion exchange, including many where a titration, with nitrate ion, of an ion-paired complex containing an anion without an absorption band in the near ultraviolet (chloride, bromide or perchlorate) was carried out. Other anions with such absorption bands were also investigated; these included nitrite and pyruvate. Impetus was thus given to an effort to synthesize chiral macrocyclic polyethers, possessing at least one axis of symmetry to keep their two faces equivalent, and without a chromophore in the near UV. Ultimately six were prepared, all with methyl substituents, two in the 15-crown-5 (13,14) family and four in the 18-crown-6 (15-18). These six compounds were the substrates for most of the research carried out over the final three-year period of the contract. The circular dichroism of ion-paired metal nitrate complexes in solution is the subject of two papers in press, crystal structures of several alkali metal and alkaline earth metal nitrates were carried out at Oklahoma State. (Several were found to be disordered.) Ammonium nitrate complexes of the 18-crown-6's were prepared and ion-pairing through hydrogen bonding was established by CD spectroscopy. Multinuclear nmr spectroscopy of several complexed cations was carried out and Raman and infrared absorption as well. Molecular mechanics calculations served to correlate spectral evidence with the calculated conformational energies.

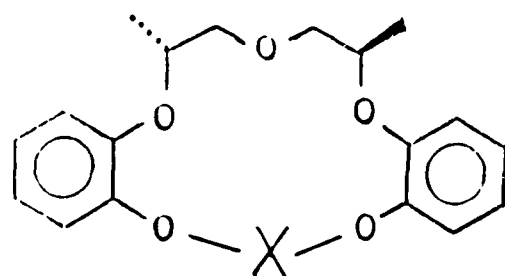
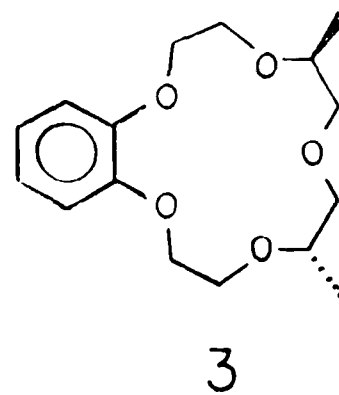
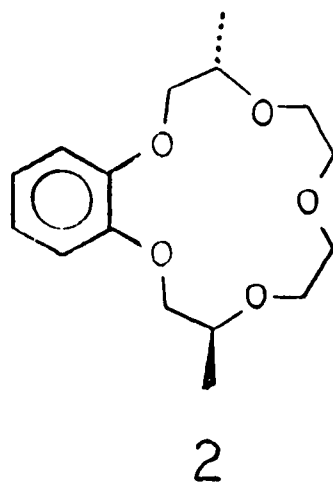
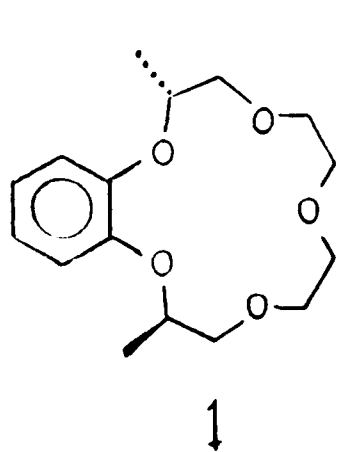
#### Circularly Polarized Luminescence of Lanthanide Complexes

Efforts to investigate systems where the metal cation provides the chromophore, to be dissymmetrically perturbed by the complexand, centered on the lanthanides as ions which form stable complexes with the 18-crown-6 and 15-crown-5 system. Unfortunately the  $f \rightarrow f$  bands are weak, circularly polarized luminescence in conjunction with total luminescence measurements (using terbium and europium chlorides, nitrates and perchlorates) proved to be rich with information about the nature of the species present in a variety of solvents. A key species is the one in which one lanthanide cation is surrounded by a macrocycle and complexed further by two bidentate nitrate ions, and carries a resultant single positive charge. Explanations of the data in terms of configurational and conformational effects have been provided in one published paper (Inorganic Chem 1985, 24, 634), one more in press, and others in preparation.

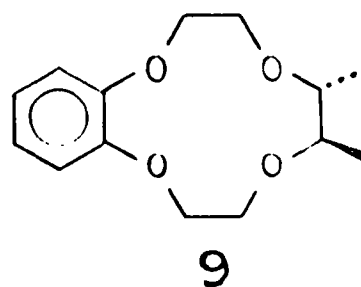
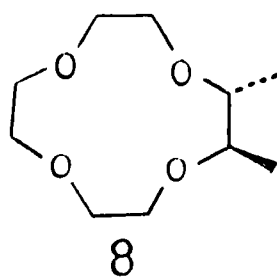
#### Other Studies

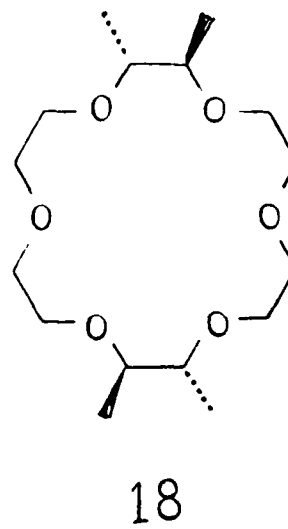
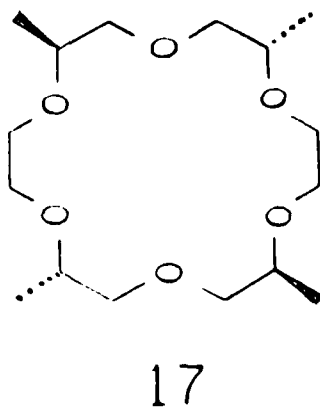
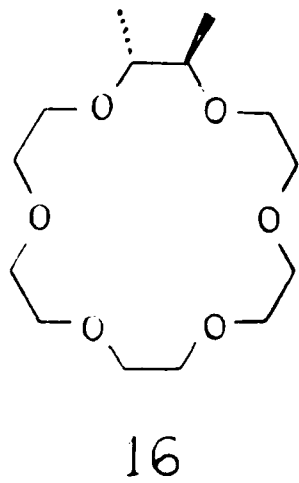
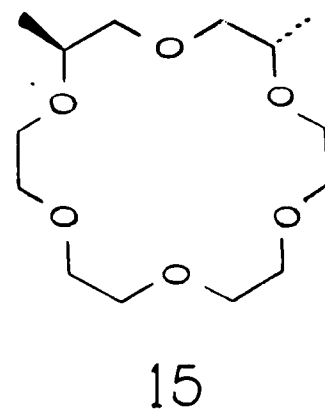
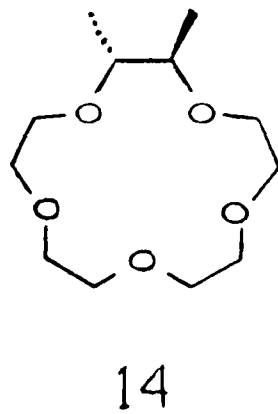
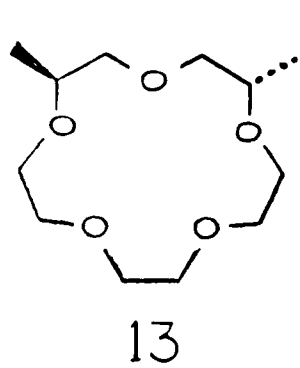
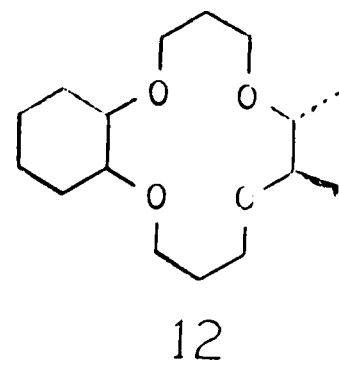
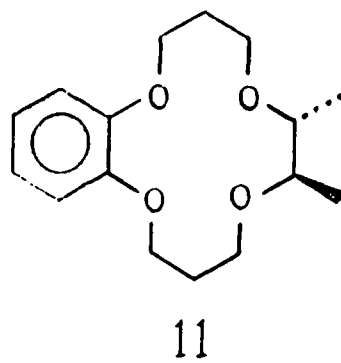
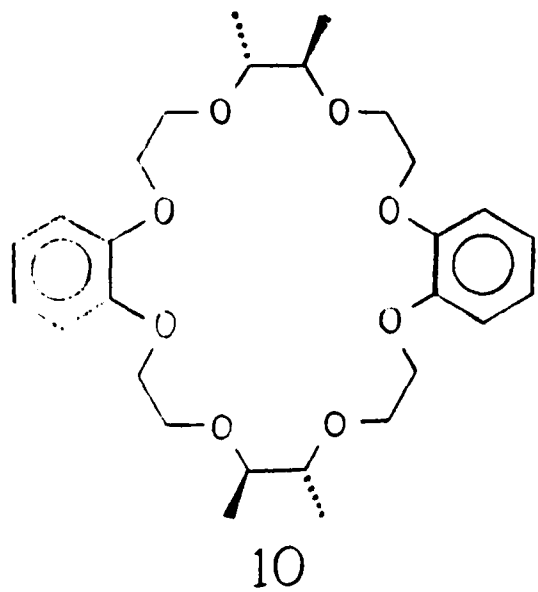
One other research task has been based on the observation that the reaction of an alkyl halide or sulfonate with nitrite ion can be accelerated and the nitrite-nitro product ratio affected if the nitrite salt (potassium or barium) is present as a macrocyclic polyether complex. A final project has involved determining the CD of a set of pyridine-containing macrocycles prepared in the laboratory of J.S. Bradshaw of Brigham Young, one of them from a diol provided by us. Sector rules have been devised to explain the CD results, which were also corroborated using (proton) nmr. A manuscript reporting this work is about to be submitted.





- X =
- 4  $(CH_2)_3$
- 5  $CH_2CH_2OCH_2CH_2$
- 6  $CH_2(CH_2OCH_2)_2CH_2$
- 7 
CC(C)COCC





END

DTTC

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